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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,277	07/25/2006	Guoqiao Li	13796-00002-US	4870

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CONNOLLY BOVE LODGE & HUTZ, LLP
P O BOX 2207
WILMINGTON, DE 19899

EXAMINER	
ARNOLD, ERNST V	

ART UNIT	PAPER NUMBER
1616	

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05/08/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,277	LI ET AL.	
	Examiner	Art Unit	
	ERNST V. ARNOLD	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 3 and 4 are new. Claims 1-4 are pending and under examination. Applicant's amendments have necessitated a new ground of rejection. Accordingly, this Action is FINAL.

Comment: In claim 2, "ration" appears to be a misspelling of ratio. Please correct.

Withdrawn rejections:

Applicant's amendments and arguments filed 3/16/09 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed below is herein withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

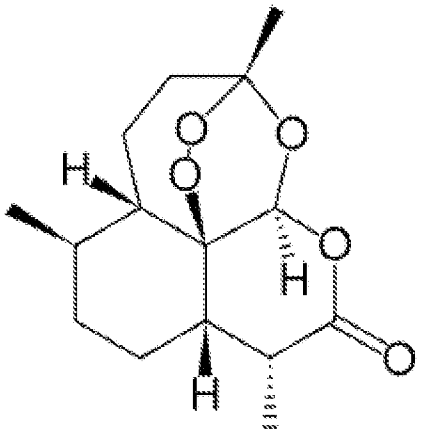
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Giao et al. (Poster Abstract International Symposium on Malaria Control in the Mekong Region Dec 10-13, 2002) in view of Abstract of EP0290959 and White (Phil Trans R Soc Lond B 1999, 354, 739-749) and Lai et al. (US 2004/0058981) and Klayman (Science 1985, 228(4703), 1049-1055).

Applicant claims a combination comprising artemisinin 1 part, piperaquine 5 parts, and primaquine less than 0.05 parts.



Artemisinin

Determination of the scope and content of the prior art

(MPEP 2141.01)

Giao et al. teach the combination of **dihdyroartemisinin, piperaquine**, trimethoprim and **primaquine** (Abstract).

Abstract of EP0290959 teaches combinations of **artemisinin**, dihydroartemisinin or other artemisinin derivatives with one or more of the antimalarials including **primaquine** (Abstract).

White teaches the use of combinations of antimalarials to overcome parasite resistance and to *always* use a combination with **artemisinin** or one of its derivatives (Abstract and page 746, (n)-(p)). White teaches the concept of triple combinations of antimalarials and that artemisinin and its derivatives have been combined with other antimalarials and have accelerated recoveries, increased cure rates, reduced transmissibility and appear to have delayed the development of further resistance and reduced incidence of disease (page 746, (n)).

Lai et al. teach the equivalence of **dihydroartemisinin and artemisinin** (claim 1, 2, 4). Lai et al. teach powders and tablets (claim 9) as well as suppositories ([0037]), suspensions ([0035]), syrups and granules ([0032]) that can be formulated.

Klayman teaches that **artemisinin** has been known in traditional Chinese medicine as a treatment for fever and malaria for many centuries (Abstract). Klayman teaches that **dihydroartemisinin** is more potent than **artemisinin** (Derivatives of QHS, left column, page 1053).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

1. The difference between the instant application and Giao et al. is that Giao et al. do not expressly teach the artemisinin and the other components in the instantly

claimed ratio of components. This deficiency in Giao et al. is cured by the teachings of Abstract of EP0290959, Lai et al., Klayman and White.

2. The difference between the instant application and Giao et al. is that Giao et al. do not expressly teach the composition in various formulations for pediatric use and wherein the primaquine can be formulated into a separate tablet to be taken along with a tablet of mixed artemisinin and piperaquine. This deficiency in Giao et al. is cured by the teachings of Lai et al.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use artemisinin, as suggested by Lai et al. and White, in the composition of Gaio et al. and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because White says to *always* use artemisinin in combinations and Lai et al. establish that artemisinin and dihydroartemisinin are functional equivalents. However, from the teachings of Klayman, it is known that dihydroartemisinin is more potent than artemisinin and therefore an adjustment of the amount of ingredients would be required to maintain the same efficacy. This is then simply a matter of routine optimization to arrive at the instantly claimed 1 part artemisinin to 5 parts piperaquine to less than 0.05 parts primaquine, which can read on 0 parts primaquine. The amount of a specific

ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention.

2. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was make different formulations for pediatric use, as suggested by Lai et al., in the composition of Gaio et al. and wherein the primaquine can be formulated into a separate tablet to be taken along with a tablet of mixed artemisinin and piperaquine and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Lai et al. establish the types of formulations one of ordinary skill in the art can formulate artemisinin. Pediatric use is intrinsic to the composition. Regarding the formulation of primaquine into a separate tablet and taken with a mixed tablet of artemisinin and piperaquine, it is the Examiner's position that formulation of the actives into one or more tablets is merely a design choice by one of ordinary skill in the art in the absence of evidence to the contrary.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to arguments:

The Declaration under 37 CFR 1.132 filed 3/16/09 is insufficient to overcome the rejection of claims 1 and 2 based upon Giao et al. (Poster Abstract International Symposium on Malaria Control in the Mekong Region Dec 10-13, 2002) in view of Abstract of EP0290959 and White (Phil Trans R Soc Lond B 1999, 354, 739-749) and Lai et al. (US 2004/0058981) and Klayman (Science 1985, 228(4703), 1049-1055) as set forth in the last Office action because: of the following analysis. Applicant asserts that clinical trials were performed with the present combination and a comparative formulation of dihydroartemisinin and piperaquine which supposedly shows a decrease in adverse side effects. Respectfully, the Examiner cannot agree. First of all, the amount of each component in the combination tested is unknown. Claim 1 allows for 0.0 parts of primaquine. From MPEP 716.02(b) [R-2] Burden on Applicant III: Evidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims. See *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) and MPEP § 716.02(d) - § 716.02(e). Second of all, it is unknown how much was given to each subject. For example, if only 100 mg of the instant combination was given to the subject

and compared to 1000 mg of the prior art sample given to the subject then is it not expected that the subject receiving the higher dose of drug would experience more side effects? Stated another way, from MPEP 716.02(b)[R-2] Burden on Applicant I: "The evidence relied *>upon< should establish "that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance." *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). There is simply no regard to dosage amounts, dosage regimens, or size of the study. Third of all there are no statistical data for analysis to see if there is overlap of the side effects. For at least these reasons the Declaration is not persuasive and the Examiner maintains the rejection. All the components are taught for the same purpose and would be expected to function as a combined anti-malarial.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ernst V. Arnold whose telephone number is 571-272-8509. The examiner can normally be reached on M-F (7:15 am-4:45 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Ernst V Arnold/
Examiner, Art Unit 1616